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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,183	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19-32,34,39-43 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19-32,34,39-43 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 09/19/2005. Pursuant to the most current listing filed 09/19/2005, claims 17, 19, 24, 25, 20-32, 34, 39-43 and 45-49 (claims 47-49 new) are currently pending and under consideration in this action. All objections/rejections not repeated herein are hereby withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/12/2005 and subsequent amendments filed 09/19/2005[1] are entered.

Priority

The earliest priority documents to which Applicant claims a benefit of priority, fail to adequately support certain claimed embodiments as follows. The priority document US 60/126,800 (filed 03/30/1999) does not fully support the instant independent claim 17. Hereinafter, in discussing support for particular angiogenic factors (e.g., claim 10 and claim 17), it must be remembered the priority issue is addressed within the context of the claimed method (i.e., enhancing blood vessel formation").

[1] This copy of the claims is the most recent thus the version that is currently examined.

Claim 17 is directed to angiogenic factors such as endothelial PAS domain protein 1 (EPAS1), monocyte chemoattractant protein (MCP-1), granulocyte-monocyte colony stimulatory factor (GM-CSF), PR39, nitric oxide synthase (NOS) and hypoxia inducing factor-1 (HIF-1), none of which are supported in provisional application 60/126,800 ('800 application). The '800 application does provide support for fibroblast growth factor 1 and 2). (e.g., Specification, p. 2, last ¶). Thus a claim that is exclusively directed to **FGF1 or FGF2** would be granted the priority date **03/30/1999**. However, the where a disclosure recites "FGF factors" generically, such a description does not provide sufficient support for all potential members, i.e., all particular FGF factors. Therefore, claims directed to additional species members, which are not recited in priority document are granted priority to the instant application's filing date (e.g., Specification, p. 13, ¶ 0040; describing FGFs 1 to 5).

Furthermore, as to the list of angiogenic factors recited in claim 17, it appears HIF-1 is supported in US provisional 60/138,379 (filed 06/06/1999). Thus, for a claim that is exclusively directed to **HIF-1** the priority date granted is **06/06/1999**.

Regarding **MCP-1, EPA1, GM-CSF** the earliest priority document that provides adequate support is US 09/868,411 (e.g., '411 application, Specification, p. 28). Therefore claims directed exclusively to any of said factors would be granted the priority date **03/30/2000**.

With respect to any claims that are directed to either **PR39 or NOS**, the claims are granted priority to the filing date of instant application, because the claims encompass embodiments that are not supported in any of the cited priority documents. Thus any claim that is directed **PR39 or NOS**, notwithstanding the fact that said claim may encompass additional embodiments disclosed in a earlier priority document, is granted the date of the instant application – **7/10/2003**.

In addition, with respect to the embodiment of **adenoviral-transfected early attaching cells**, there is no sufficient support in any of the priority documents. The priority documents are limited to generic descriptions of what is known in the relevant art, such as direct administration of adenoviral vectors encoding a transgene (e.g., US 60/138,379, p. 2, top), delivery of an end-product angiogenic factor via gene transfer (US 60/126,800, p. 2, ¶ 2), or indicating that use of adenovirus-mediated delivery of angiogenic factors is an "open issue" (US 09/868,411; p. 2, l. 25). Thus, it is only in the instant application that there is support for utilization of transfected early attaching cells, wherein said cells are transfected with an adenoviral vector encoding an angiogenic transgene (e.g., p. 14, ¶ 0044, discussing "early attaching cells" from the bone marrow; p. 16, ¶¶ 0050-51, discussing viral vectors including adenoviral vectors; pp. 34-35, Example 7, providing a prophetic example for *in vivo* administration of transfected cells; pp. 37-38, Example 8, teaching an *in vitro* transfection of early attaching cells to demonstrate enhanced angiogenesis *in vitro*; p. 39, ¶¶ 0124-27, teaching *in vivo* administration of transfected cells in a mouse model of hindlimb ischemia). Thus, as matter of fact, only the instant disclosure provides support for the claimed methods.

In view of the foregoing, all the claims under consideration, **claims 3-12, 17, 24-25, 29, 30-32, 34, 39-43, 45 and 46-49,** are granted priority to the instant application's filing date – **07/10/2003**.

Claim Objections

Claim 47 is objected to for comprising a typographical error (i.e., sentence ends with two periods). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 3, 9-12, 17, 19, 24, 25, 29-32, 34, and 47-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claims 3 and 9-12 are dependent from base claims that are cancelled. As such, it is unclear to what subject matter the rejected claims are directed.

Independent claim 17 recites the phrase "which cells have been transfected with an adenoviral vector", but as written, it is unclear whether the limitation "which cells" is delimiting the "early attaching cells" or the population of cells that necessarily comprise "autologous bone marrow". It would be remedial to insert the term "early attaching" in the limitation "which [early attaching] cells", if this is what is intended.

In addition, as written, claim 17 is vague and indefinite because it is unclear at what point the target cells are transfected (e.g., *in vitro*, *in vivo* or *ex vivo*).

For example, as written the claim can be interpreted as directed to *in vivo* transfection, or to *in vitro* transfection. However, this is not a case where the claim is merely broad, because depending on which alternative interpretation is adopted the claimed method is defined by biologically and patentably distinct boundaries. For example, bone marrow cells comprise several population of cells, including those with the inherent property of being "early attaching cells" when cultured. Indeed, even "early attaching cells" are not limited to a single uniform population of cells. In any event, as written claim 17 reads on transfection of such cells *in vivo*,

such as through administering a viral vector to an animal subject, where the steps involved include delivery of the vector into the bone marrow and transfection of target cells, which steps require wholly distinct or at least additional or substantive considerations regarding the prior art as well as 35 U.S.C. § 112, first paragraph. Without further clarification, the claims' metes and bounds are indeterminable.

Claim 25 recites, "culturing of the bone marrow" which lacks sufficient antecedent support in base claim 17. As written the claim is directed to a culturing step in base claim 17, where no such step is recite in the base claim. Furthermore, since bone marrow comprises "early attaching cells" whether cultured or not, claim 17 is not directed to a culturing step merely by reciting "early attaching cells" (e.g., aspirate comprising both cells that are nonadherent or adherent, were such cells to be cultured). Thus, the claim's metes and bounds are indeterminable.

Claims 29-32 recite the limitation "the agent" which lacks sufficient antecedent support in base claim 17. In addition, claim 49 recites "the composition" which lacks sufficient antecedent support, because it is not clear to what composition claim 49 is directed. For example, claim 17 recites multiple limitations that can be construed as a "composition" (e.g., cells, bone marrow, adenoviral vectors). As such, the claim is vague and indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. **Claims 39-43 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwaguro et al. (Circulation, 2002; 105:732-38), in view of Hamawy et al. (Curr. Opin. Cardiol. 1999; 14:515-22), and further in view Hristov et al. (Arterio. Thromb. Vasc. Biol. 2003; 23:1185-89) and Tomita et al. (Circulation, 1999; 100(supp. II):247-56) .**

Regarding claim 42, the limitations for the step of stimulation of cells with hypoxia is deemed of little moment in determining the claimed composition versus a composition taught in the relevant art meeting the limitations defining said composition (e.g., "early attaching cells obtained from bone marrow, transfected with adenoviral vector"). In other words, absent evidence to the contrary where the prior art teaches that it would have been obvious to make a certain modification to produce a certain product, how that product is manipulated (e.g., stimulated) does not necessarily distinguish a claimed product. Similarly, limitations that characterize how the claimed product is used (i.e., intended use) do not distinguish the claimed product from an anticipatory product. (i.e., claim 46). By analogy, it is important to note that manipulations to a product are of little moment with respect to patentability of said product.

Therefore when a reference teaches a product that appears to be the same or an obvious variant of the product set forth in a product-by-process claim although produced (or manipulated) by a different process, then said reference anticipates the claim. *See In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983); *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985); *See also*, MPEP § 2113.

In addition, the limitation "early attaching cells" is not particularly or exclusively defined in the disclosure thus is interpreted as broadly as reasonable to mean any cells from bone marrow or from culture medium containing bone marrow, which cells may include monocytes, endothelial precursor cells (EPCs) or any other hematopoeitic lineage cells, and where said cells do not wash away after about 8 to 24 hours of growth under suitable culture conditions. (e.g., Specification, p. 14, ¶ 0044).

Iwaguro et al. teach a composition comprising transfected progenitor endothelial cells (EPCs) obtained from bone marrow. The cells are transfected with an adenoviral vector-encoding gene for vascular endothelial growth factor (VEGF). (e.g., p. 733, col. 1; p. 734, col. 1, last ¶) (claim 39: transfected with adenoviral vector). An intrinsic property of EPCs is that in culture the cells are adherent (i.e., early attaching). For example, Hristov teaches that progenitor endothelial cells (EPCs) for angiogenesis can be isolated from bone marrow. (Hristov et al. Arterios. Thromb. Vasc. Biol. July 1, 2003; 23:1185-89; e.g., p. 1187, col. 1, last ¶).

Furthermore, Hristov teaches that classically utilized methods of isolation include use of adherence culturing techniques, i.e., isolating adherent or attaching cells. (Id.)(claim 39: early attaching cells). The salient point is the EPCs are the same in characteristics as to being adherent cells in culture, whether said EPCs are obtained from bone marrow or peripheral blood. In other words, the source of the EPCs is bone marrow in the first place, as evidence by Iwaguro and

Hristov. In sum, Iwaguro demonstrates that *ex vivo* expansion and transfection with an angiogenic factor promotes neovascularziation of ischemic tissues, including limb muscle. (e.g., p. 736, col. 2, ¶ 2).

Iwaguro does not explicitly teach the said cells can be transfected with any of the recited angiogenic factors (i.e., HIF-1, EPAS1, MCP1, GM-CSF, PR39, FGF or NOS). In addition, Iwaguro does not teach that the composition can further contain an anticoagulant, such as heparin.

Each one of the foregoing limitations to which Iwaguro does not explicitly speak, are addressed in turn. First, with respect to additional transgene angiogenic factors, one of skill will recognize that many angiogenic factors were well recognized for their properties and well before the Iwaguro publication thus as potential candidates for gene transfer to bone marrow-derived early attaching cells such as EPCs that Iwaguro teach.

As a matter of fact in discussing therapeutic angiogenesis and gene therapy strategies for revascularization of ischemic muscle tissue (e.g., myocardial), Hamawy et al. teach that over 20 angiogenic factors are identified in the prior art. (e.g., p. 516, col. 2, Table 1). Indeed, the list of angiogenic factors includes the VEGF that Iwaguro teaches, as well as FGF(s) as recited in claim 39. (Id.). Furthermore, Hamawy discusses that gene therapy vectors can include several well-characterized systems, including that of adenovirus. (e.g., p. 517, Table 2, and col. 2, last ¶ bridging to p. 518).

Therefore, it would have been obvious to modify the adenoviral vector as taught by Iwaguro with one of several additional angiogenic factors that were known in the art, as taught by Hamawy, such as FGF(s). One would have been motivated to make such a modification to expand the range of potential therapeutic angiogenic factors that can be utilized in effecting

therapeutic angiogenesis. Further, given the level of skill in the art at the time of invention, it would entail nothing more than routine steps to mobilize a different gene (e.g., encoding an FGF) into the adenoviral vector as taught by Iwaguro.

With respect to a composition of cells obtained from bone marrow further comprising an anticoagulant, such an addition is routine in the art when obtaining cells from bone marrow (e.g., to prevent coagulation/clotting of marrow-derived cells, etc.). Further, there is no evidence of record that indicates addition of an anticoagulant to a composition of bone marrow-derived cells is inventive. Indeed, Tomita et al. teach that obtaining bone marrow derived cells (i.e., through aspiration) it is beneficial to have an anticoagulant present. (e.g., p. 247, col. 2, last ¶ bridging to p. 248).

Therefore, in obtaining EPCs for *ex vivo* expansion, where said cells are obtained from bone marrow as taught by Hristov, it would have been obvious to add heparin to the aspirate so as to obtain the benefit of preventing coagulation/clotting of cells in the marrow aspirate, as is taught by Tomita. Given the level of skill in the art at the time of invention, it would have been remedial to add the component of an anticoagulant to a composition comprising bone marrow, which in turn comprises cells that are expanded/transfected *ex vivo*.

3. **Claims 17, 24, 29, 30, 34, 39-43 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwaguro et al. (Circulation, 2002; 105:732-38), in view of Hamawy et al. (Curr. Opin. Cardiol. 1999; 14:515-22) or Isner et al. (US 6,569,428; see entire document), and further in view Hristov et al. (Arterio. Thromb. Vasc. Biol. 2003; 23:1185-89) and Tomita et al. (Circulation, 1999; 100(supp. II):247-56) .**

The claims are interpreted consonant with what is stated above. In addition, the limitations "injecting" or "injected" are interpreted as broadly as reasonable, since no exclusive definition is provided, to include transplantation of cells into ischemic tissue. Furthermore, as interpreted above, the teachings of Iwaguro and Hamawy are incorporated and applied herein by reference.

In sum, Iwaguro teaches a method of transplanted adenoviral transfected EPCs into ischemic muscle tissue (hind limb) to effectuate collateral blood vessel formation. (e.g., p. 733, col. 2, ¶ 2). In lieu of repeating that which has already been discussed, it would have been obvious to modify the adenoviral vector to express additional angiogenic factors, such as FGF. (Supra, Rejection No. 2). Furthermore, the reference teaches that 100ul of EBM-2 medium (in which cells are expanded *ex vivo*, i.e., "conditioned") along with the transfected EPCs therein are administered to ischemic tissue systemically through the tail vein. (Id.)(claims 17, 34, 47).

Thus Iwaguro does not teach directly injecting said cells into the ischemic target site. Furthermore, regarding effective amounts of about 0.2 to about 0.5 ml of the composition in from about 12 to 25 sites as recited in 49, said limitations are interpreted as broadly as reasonable in light of the delimitations based on the term "about", to include amounts less than 0.2 to 0.5 ml (e.g., 0.1 ml) and to sites less than 12 to more than 25 (e.g. 1 to 40). Such an interpretation is reasonable, because the limitation "about" is broad and open-ended.

As to injecting directly into target sites, many suitable means of delivering cells, such as cells to promote angiogenesis, are routinely utilized in the prior art. For example, Isner teaches that progenitor cells can be obtained from human bone marrow (e.g., col. 6, ll. 57-60), that said progenitor cells can be genetically modified to express secreted angiogenic factors such as VEGF, GM-CSF or FGF (e.g., col. 8, ll. 36-55) via viral vectors (e.g., col. 7, ll. 40-45) to

effectuate angiogenesis. (e.g., col. 8, ll. 16-18). Thus either Isner or Hamawy teach that various angiogenic factors can be utilized to transfect progenitor cells in methods of promoting collateral blood vessel formation in ischemic tissue. Further, Isner teaches that administration can be through site directed such as through bolus injection or catheter. (e.g., col. 7, ll. 22-27). Thus, it is clear that the route of administration of transfected progenitor cells is not inventive, but rather, quite remedial.

Thus, it would have been obvious to modify the method of systemic delivery that Iwaguro teaches to one of site directed injection, that Isner teaches. One would have been motivated to make such a modification to maximize the potential of transfected cells excreting therapeutic angiogenic factors in the ischemic target tissue, versus relying on some of the cells being deposited in the target site via systemic delivery. Given the level of skill in the art at the time of invention, it would entail nothing more than remedial steps to utilize site directed injection, versus systemic delivery. Thus there would have been a reasonable expectation of success to use a route of administration as taught by Isner to modify the systemic delivery as taught by Iwaguro.

Regarding multiple sites, or determining dosage amounts, including number of sites for injection (i.e., claims 48-49), as Iwaguro teaches, it is routine to conduct preliminary experiments, to determine dose-dependent (i.e., efficacious amounts/sites) administration of transfected EPCs, to determine the minimum number of cells to be utilized. Moreover, it is recognized that, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Therefore, it would have been obvious to determine workable amounts and the number of sites based on the amounts of cells to be administered, in a method of injecting transfected EPCs as collectively taught by Iwaguro and Isner. One would have been motivated to conduct such routine and preliminary experimentation to determine for a given angiogenic factor what is a workable amount of cells (e.g., 100ul to 1ml), and based on said amount would determine the volume to inject thus determining a workable number of injection sites. Given the level of skill in the art at the time of invention, it would have been routine to optimize amounts/sites of injection in methods of effectuating collateral blood vessel formation as taught by Iwaguro and Isner. Thus there would have been a reasonable expectation of success to conduct preliminary experiments to determine the amount of cells/medium to be injected and thus the number of sites.

4. **Claims 17, 19, 24, 29, 30, 34, 39-43 and 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwaguro et al., Hamawy et al. or Isner et al., and further in view Hristov et al., Tomita et al. and further in view of Furcht et al. (US 2005/0181502 A1, see entire document).**

Additional limitations (claims 19 and 45) are directed to the early attaching cells as being *marrow stromal cells* (MSCs). The specification provides an exclusive definition that limits MSCs to CD34 minus/CD45 (CD34/CD45-)minus cells. Further, the claims are interpreted consonant with what is stated above.

As interpreted and discussed above, the teachings of the Iwaguro et al., Hamawy et al. or Isner et al., and further in view Hristov et al., Tomita et al. are applied and incorporated herein by reference; none of said references explicitly teach that early attaching cells are CD34/CD45-cells.

However, with respect to "marrow stromal cells", it must be noted that where early attaching cells are isolated from bone marrow, the cells are not homogenous in character. In other words, if EPCs are obtained from bone marrow and expanded *in vivo* (as taught by Iwaguro and Hristov, supra), the adherent cells that are cultured would be heterogenous in nature, which heterogenous cells share the characteristics of adherence to plastic (e.g., culture dish). (See, Prockop, Science, 1997; 276:71-74, e.g., p. 72, col. 2, ¶ 1; discussing an intrinsic property of marrow stromal cells)[2]. Further, MSCs can during the course of culturing differentiate insofar as what cell markers are expressed, e.g., CD34, CD45. For example, in a culture of early-adhering cells, CD34-negative angioblasts may be a subset of a broader genus of monocytic cells, which monocytes have the potential to progress to EPCs. (Supra, Hrsitov, 2003, p. 1186, col. 1, ¶ 1). In other words, the milieu of cells obtained from bone marrow that are early attaching cells comprises a mixed population of cells that would comprise CD34+/- and CD45 +/- cells. Alternatively, as Hristov teaches the same cell population under different conditions may express different sets of cell markers (e.g., CD34+ under one set of conditions but CD34- under other conditions), with the salient point being that it is an inherent characteristic of marrow stromal cells to express the same cell markers differentially. In sum, the EPCs as taught by Iwaguro and Hristov would reasonably be expected to contain some cells that are CD34/CD45-.

Alternatively, Furcht teaches that multipotent cells that are isolated from marrow and that do not express (or are negative) for surface antigens CD45, in addition to CD34. (e.g., , ¶ 0020; ¶¶ 0065-67, 0075). The reference refers to such cells as multipotent adult stem cells (MASCs). Further, the reference teaches that such cells can be transfected to express a target DNA, such as with viral vectors. (e.g., ¶ 0023). The reference teaches that such cells are more beneficial in

[2] This reference is merely being provided as background for the term "marrow stromal cell" as used in the art.

therapeutic applications, because as progenitor cells, they are able to differentiate into a wide variety of cell types, including endothelial cells. (e.g., ¶ 0019; Fig. 9).

Therefore, it would have been obvious to utilize such cells in methods of effectuating collateral blood vessels as taught by Iwaguro and Isner. One would have been motivated to make such a modification to obtain the benefit of cells that would readily express and excrete the target therapeutic protein and would be capable of forming endothelial cells thus expanding the range of bone marrow cell populations that can effect collateral blood vessel formation. Given the level of skill in the art at the time of invention, there would have been a reasonable expectation of success to substitute the EPCs with MASCs as taught by Furcht, given that only routine steps would be required for isolating said MASCs (e.g., it would be remedial to utilize adenoviral vectors to transfect said cells).

5. **Claims 17, 19, 24, 29, 30-32, 34, 39-43 and 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwaguro et al., Hamawy et al. or Isner et al., and further in view Hristov et al., Tomita et al. Furcht et al., further in view of Smith et al. (Arter. Thromb. Vasc. Biol. 2002; 2:1279-85) and Li et al. (Nat. Med. 2000; 6:49-55).**

Additional limitations are directed to the factors NOS and PR39 as the angiogenic proteins expressed from the adenoviral vector-transfected early attaching cells. As interpreted and discussed above, the teachings of the Iwaguro et al., Hamawy et al. or Isner et al., and further in view Hristov et al., Tomita et al. and Furcht are applied and incorporated herein by reference; none of which explicitly teach utilizing NOS or PR39.

However, the evidence in the prior art teaches that said NOS and PR39 proteins are recognized as factors that promote angiogenesis. For example, Smith teaches a method of

utilizing an NOS-encoding adenovirus vector in a method of promoting angiogenesis in a rat model of hindlimb ischemia. (e.g., Abstract; p. 1280, col. 1, under Methods; p. 1282, Fig. 2; p. 1283, col. 2, ¶ 2). The salient teaching is that NOS is one of yet another host of angiogenic factors.

In addition, Li teaches that the peptide PR39 through its effects on HIF1 protein vis-à-vis preventing degradation results in promotion of collateral blood vessel formation. (e.g., Abstract; p. 49, col. 2, ¶ 2; p. 50, col. 2; p. 52, Fig. 3). Once again, the salient teaching is that PR39 is another angiogenic factor that is shown to promote angiogenesis.

Therefore, it would have been obvious to modify the adenoviral vector encoding VEGF as taught by Iwaguro, to instead encode either NOS or PR39 as taught by Smith and Li, respectively. One would have been motivated to make such modification to extend the range of therapeutic angiogenic factors in a method of treating muscle ischemia as taught by Iwaguro and/or Isner. Further, given the level of skill in the art at the time of invention there would have been a reasonable expectation of success in replacing one angiogenic factor with another.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,
Ray Akhavan/AU 1636

DANIEL M. SULLIVAN
PATENT EXAMINER